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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,776	12/19/2005	Meir Shinitzky	74127/JPW/JW	9387

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EXAMINER	
SHTERENGARTS, SAMANTHA L	
ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,776	SHINITZKY ET AL.	
	Examiner	Art Unit	
	Samantha L. Shterengarts	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-72 and 135-212* is/are pending in the application.

4a) Of the above claim(s) *49-72,135-164,169-180 and 186-212* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *165-168 and 181-185* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7Apr05, 20Dec05, 23Apr07, 27Oct08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The instant application is a national stage entry of PCT/IL03/0820, filed October 9, 2003, which claims priority to U.S. Provisional application no. 60/417,157, filed October 10, 2002.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on April 7, 2005, December 20, 2005, April 23, 2007, and October 27, 2008 were in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS documents were considered. A signed copy of each form 1449 is enclosed herewith.

Election/Restrictions

3. Applicant's election with traverse of Group VII, Claims 165-185 in the supplemental reply filed on January 16, 2009 is acknowledged. The traversal is on the ground(s) that method of use claims of Group I should be examined along with the elected product claims. This is not found persuasive for the following reasons.

An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a)

Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Groups I-IX lack unity of invention since under 37 CFR 1.475: the technical feature corresponding to the claims is the O-CO moiety. This is the core technical feature because it is the only non-variable core that is common to all compounds of formula (I). This core technical feature is not a special technical feature because it fails to define a contribution over the prior art, as can be seen in the U.S.C. 103 rejection below.

Therefore, claims 49-72 and 135-212 are not so linked as to form a single general inventive concept and there is a lack of unity of invention because they lack a special technical feature as the technical feature present fails to define a contribution over the prior art. The core technical feature that is being claimed is taught by the prior art. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

Furthermore, in regards to Groups I-IX, even if unity of invention under 37 CFR 1.475(a) is not considered lacking, which it is as evidenced above, unity is lacking under 37 CFR 1.475(b). Under 37 CFR 1.475(b): A national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of said product, and a use of said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of said product, and an apparatus or means specifically designed for carrying out the said process.

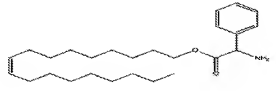
And according to 37 CFR 1.475(c): if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph 37 CFR 1.475(b), unity of invention might not be present.

Therefore, since the claims are drawn to compounds and compositions, which do not make a contribution over the prior art, as well as *various* methods of using the compounds, as in claims 49-72, 135-164, and 186-212, and according to 37 CFR 1.475(e): the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claims.

Therefore, since the claims do not relate to a single general inventive concept under PCT Rule 13.1 and lack the same or corresponding special technical feature, the claims lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

4. As per MPEP 803.02, the Examiner will determine whether the entire scope of the claims is patentable. Applicants' elected species of the following compound does not make a contribution over the prior art:



Therefore, according to MPEP 803.02: should the elected species appear not allowable, the Markush-type claim shall be rejected and claims to the nonelected invention held withdrawn from further consideration. It has been determined that the entire scope claimed is not patentable.

Status of the Claims

5. Currently, Claims 49-72 and 135-212 are pending in the instant application. Claims 49-72, 135-164, 169-180, and 186-212 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention and species. Claims 165-168 and 181-185 read on an elected invention and species and are therefore under consideration in the instant application insofar as they read on the elected species above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 184 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Nature of the Invention

Claim 184 is drawn to a pharmaceutical composition for the treatment of inflammation.

The State of the Prior Art and the Predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instantly claimed invention is highly unpredictable as discussed below: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of the above listed class of inflammatory diseases, whether or not the disease is affected by the instantly claimed compounds.

With regards to methods of treating and preventing inflammatory disorders, the diseases are too divergent and require different methods of treatment. Examples of disorders associated with inflammation include, but are not limited to: asthma, autoimmune diseases, chronic inflammation, chronic prostatitis, glomerulonephritis, hypersensitivies, inflammatory bowel diseases, pelvic inflammatory disease, reperfusion injury, rheumatoid arthritis, shoulder tendonitis, transplant rejection, vasculitis, and various allergies. This broad list of diseases each has a different cause, and for the majority of the list, a different treatment. There is not one class of compounds, let alone one compound, which can treat all of these diseases.

For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually in any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Accordingly, treatments for inflammation can normally be tailored to the particular type of inflammation present, as there is no, and there can be no, "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilation and leaking of vessels. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. There are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. This discussion, demonstrates the extraordinary breadth of the causes, mechanisms, and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to accept any agent for treatment and prevention of inflammation generally. Applicant's disclosure does not enable one of ordinary skill in the art to make or use the claimed invention within the entire scope of the diseases listed above. There is no compound, let alone entire classes of compounds, that can reverse, alleviate,

prolong the progression of, prevent, or treat the various and divergent diseases listed above, as claimed.

The Amount of Direction / Guidance Present and the Presence or Absence of Working Examples

The specification does not contain any evidentiary support that these compounds, or their obvious variants, would be able to treat the plethora of diseases listed. Furthermore, there are no working examples to support the treatment of the instantly claimed class of inflammatory disorders.

The breadth of the claims

The claims are drawn to a method of treating inflammation. Note one compound, let alone a genus of compounds, could possibly be effective for the treatment of all of the instantly claimed diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the inventions is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compound exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment or prevention of the various diseases, as a result necessitating one of skill to perform an exhaustive search for which diseases can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention.

Only a majority of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not mean that the other diseases meet the enablement requirements.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases, out of all diseases, would be benefited by the compounds and compositions of Formula i and would furthermore have to determine which of the claimed compounds would provide treatment of which disease.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

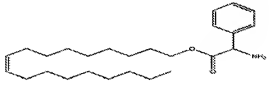
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 165-168 and 181-185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hercelin et al. (FR Patent no. 2383662) in view of Patani et al., [Patani, George A. Bioisosterism: A rational approach in drug design. *Chem. Rev.* 96 (1996) 3147-3176.]

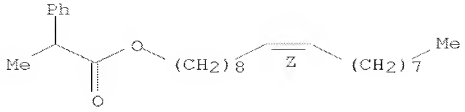
Determining the scope and contents of the prior art

The prior art reference teaches a compound that is a bioisostere of the instantly claimed elected species:



Ascertaining the differences between the instant claims and the prior art

Hercelin et al. teaches the following compound:



The reference differs from the instantly examined species insofar as it does not have a terminal amine group. However, the instantly examined species and the compound of the prior art are bioisosteres of each other.

Patani et al. teaches that that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents," and further that the concept of bioisosterism is "intuitive" (page 3147, Introduction, column 1-column 2). Bioisosteric substitutions are well-known in the art. For example, NH_2 and CH_3 are isosteric (see Table 2, column 4 and Table 12, compounds 20b and 20d; pages 3148 and 3153, respectively.)

Resolving the level of ordinary skill in the pertinent art – Prima facie case of obviousness

MPEP 2144.08.II.A.4(c) states, "…consider teachings of a preferred species within the genus. If such a species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties."

The motivation to make the instantly examined species derives from the expectation that structurally similar compounds would possess similar biological activity, and to produce a more clinically effective agent as disclosed in Patani et al. Thus, it would have had *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to be motivated to

combine the compound taught by Hercelin et al. with the disclosure on known bioisosteres from Patani et al. to interchange the secondary amine group for a methyl group with a reasonable expectation of success.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samantha Shterengarts whose telephone number is (571)270-5316. The examiner can normally be reached on Monday thru Thursday 9-6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph K. McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samantha L. Shterengarts/
Examiner, Art Unit 1626

/Kamal A Saeed/
Primary Examiner, Art Unit 1626